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Review Article

Corticosteroid Treatment in Septic Shock

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ABSTRACT

Septic shock, the most severe manifestation of sepsis, is characterized by profound circulatory failure and carries the highest mortality risk among sepsis-related conditions. Current therapeutic strategies remain primarily supportive, emphasizing empirical antimicrobial therapy and advanced organ system support. The immunomodulatory properties of corticosteroids in sepsis pathophysiology have been extensively investigated since the 1970s, though current guidelines recommend corticosteroid therapy for sepsis patients, albeit with a weak evidence base. In this review, we explore the molecular underpinnings of corticosteroid activity in septic shock and clinical evidence from randomized controlled trials, with a special emphasis on the stabilization of hemodynamics and the impact on mortality outcomes. Furthermore, we analyze recent advances in pharmacodynamic understanding that may inform more targeted corticosteroid administration in septic shock.

Keywords molecular biology, pharmacology, preclinical models, clinical trials, systematic reviews, guidelines

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Issue Theme Corticosteroids in Critically Ill Patients **Guest Editor** G. Umberto Meduri, MD, FCCP

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Septic shock is the most severe stage of sepsis, characterized by life-threatening circulatory and cellular dysfunction due to deregulated host response to invading pathogens. According to the Sepsis-3 criteria, it is defined as persistent hypotension requiring vasopressors to maintain a mean arterial pressure (MAP) ≥65 mm Hg, and elevated blood lactate (2 mmol/L) despite adequate fluid resuscitation, indicating tissue hypoxia and a high risk of multi-organ failure.[1]

Epidemiology of Septic Shock

Although the incidence and associated mortality with sepsis shock have decreased during the last two decades, it still remains the leading cause of critical illness and death worldwide, with significant age and regional variations.[2–4] Large-scale epidemiological studies showed a heavy disease burden associated with septic shock: adult ICU cohorts demonstrate an incidence of 10 to approximately 22% coupled with a devastating 30 to approximately 45% mortality rate, while pediatric populations exhibit a markedly lower incidence of 2 to approximately 8% but higher mortality rates ranging from 10 to 30%.[5–10] The prevalence and mortality rates of sepsis are significantly higher in low and middle-income countries compared with high-income countries, as evidenced by the global burden of sepsis and the impact of factors such as antimicrobial resistance, resource shortages, and limited sepsis bundle compliance. Septic shock is associated with long-term complications among survivors, such as physical dysfunction and heightened long-term mortality; moreover, the neuropsychological deficits and immune dysregulation of survivors should not be underestimated either.[9,11,12]

Septic shock is more likely to occur in the elderly, individuals with chronic underlying conditions or immunodepression, and children under the age of 5 years.[4,5] The predominant pathogen of septic shock is gram-negative bacilli, with the Asia area confronting escalating challenges due to the rising prevalence of multi-drug-resistant bacterial strains.[5,8,12] Respiratory system infections prevail as the most frequent clinical manifestations across both adult and pediatric populations, followed by abdominal and bloodstream infections.[5,12]

The treatment for septic shock relies on the control of infections and the support of organs. Early recognition and aggressive therapy are critical to improving outcomes. Since their discovery 75 years ago,[13] nearly 3% of the world population is exposed to corticosteroid therapy,[14] and they remain the mainstay of rheumatoid arthritis treatment and most inflammatory diseases.[15] Corticosteroids have played an important role in treating septic shock for over half a century; herein, we review their mechanisms of action and clinical evidence about their clinical added values.[16]

Mechanisms Relevant to Corticosteroid Treatment in Septic Shock

The pathophysiology of septic shock emanates from a triad of interconnected pathomechanisms: dysregulated host defense

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mechanisms following microbial invasion, time-dependent immune paralysis with epigenetic reprogramming, progressive microcirculatory failure leading to mitochondrial dysfunction, and sequential organ dysfunction.[3] Cortisol is a steroid hormone synthesized and released by the adrenal glands, regulated through the hypothalamo–pituitary–adrenal axis, influenced by various factors like pro-inflammatory cytokines, playing an important regulatory role in immune function under physiological conditions. Critical illness-related corticosteroid insufficiency (CIRCI) is clinically defined as insufficient cellular corticosteroid activity in critically ill patients, particularly in conditions such as septic shock. CIRCI is characterized by impaired glucocorticoid (GC)-glucocorticoid receptor (GR)-mediated transcriptional regulation, manifesting as diminished capacity to downregulate pro-inflammatory transcription factors.[17] How does exogenous corticosteroid therapy act on septic shock? The mechanism has long been controversial. In recent years, significant strides have been made in understanding the molecular and pharmacological mechanisms of sepsis treatment, particularly through the use of corticosteroids.

Molecular Mechanisms of Corticosteroid Effects

Corticosteroids passively diffuse across the cell membrane due to their lipophilic nature, binding to cytosolic GR. Unliganded GR monomer exerts as part of a multiprotein complex with chaperones such as heat shock proteins (Hsp70 and HSP90) and immunophilins (FKBP51 and FKBP52). Upon ligand binding with corticosteroids, the GR monomer undergoes conformational changes, dissociates from the chaperone complex, and forms a GR dimer. Then, the GR dimer translocates to the nucleus and directly binds to glucocorticoid response elements (GREs) on DNA, modulating gene transcription and translation.[18] It can either promote or repress the transcription of target genes, depending on the location and arrangement of GREs. Research revealed that corticosteroids profoundly influenced inflammatory, endothelial, immune, and tissue-specific responses in septic shock through a sophisticated interplay of both nongenomic and genomic effects.[18,19]

Genomic Effects: Long-Term Immune Homeostasis Regulation

GR Dimer-Dependent Gene Transactivation

Genomic effects are initiated within a few hours following exposure to corticosteroids, as the GC-GR complex translocates to the nucleus to regulate gene transcription, a process that requires time for mRNA production and protein synthesis. Genetic polymorphisms and GREs-driven gene activation events may underpin the molecular mechanisms responsible for the anti-inflammatory, immunomodulatory, and barrier-protective effects observed in septic shock. Glucocorticoid-induced leucine zipper (GILZ) is an upregulated downstream transcription factor. Research has demonstrated that NF-κB signaling, a critical pathway in inflammation, can be regulated to inhibit inflammation. This regulation has been shown to be effective in transgenic GILZ-overexpressing mice and patients with septic shock, where it not only suppresses inflammatory responses but also enhances phagocytosis, a process integral to the immune system's ability to clear pathogens and cellular debris.[20–22] Vettorazzi et al demonstrated that corticosteroids significantly alleviated inflammation in mice models of acute lung injury (ALI) by synergistically inducing sphingosine kinase 1 gene expression via GR in macrophages. This mechanism enhanced circulating sphingosine-1-phosphate production, thereby protecting the endothelial barrier function.[23] We hypothesize that corticosteroids may exert similar anti-inflammatory effects in this manner during septic shock, considering the common pathological characteristic of excessive systemic inflammatory response shared by septic shock and ALI. Furthermore, GC-GR complexes mediate the recruitment of corepressor proteins with histone deacetylase (HDAC) activity, which deacetylate core histone proteins bound to DNA, thus suppressing the transcription of inflammatory genes. Zhang et al demonstrated that HDAC2 is essential for physiological concentrations of corticosteroids to inhibit lipopolysaccharide (LPS)-induced inflammatory responses such as the production of TNF-α and IL-1β in rat cardiac fibroblasts.[24] However, this study focused on local inflammation instead of septic shock.

GR Monomer-Mediated Transrepression

When bound to ligands, GR monomers can independently associate with transcription factors like NF-κB and activator protein-1, without the need for DNA binding, thereby hindering the activation of pro-inflammatory gene transcription. GR monomers are essential for the inhibition of TNF-α, whereas the repression of interferon-stimulated genes and necroptosis-related genes in epithelial cells relies more on GR dimers.[25] Suppression of GR monomers on pro-inflammatory cytokine gene expression (TNF-α, IL-1β, IL-6, etc.) has been demonstrated in multiple cell types, including macrophages, dendritic cells, and endothelial cells.[25,26]

Cell- and Organ-Specific Genomic Regulation

Macrophages, endothelial cells, and dendritic cells form the core components of the "inflammation-coagulation-immune disorders" network in septic shock. It is suggested that GR interacts with various coactivators and corepressors to modulate chromatin structure and gene accessibility during inflammatory disease, shaping the cell-type specificity of corticosteroid genomic actions.[27,28] As discussed above, macrophage GR mediates the induction of GILZ, suppressing inflammatory kinase signaling and cytokine production.[21] Endothelial GR regulates gene expression pivotal to endothelial barrier function, suppresses NF-κB activity and nitric oxide production, thereby demonstrating a protective role in LPS-induced sepsis rat models.[28–30] Endogenous corticosteroids suppress IL-12 production via the GR-associated gene expression in dendritic cells, thereby restraining excessive IFN-γ synthesis by NK cells and delivering vital protection against septic shock, as shown by the rat model lacking GR in dendritic cells.[31] In addition to these cell-specific GR, the organ-specific hepatic GR signaling is important for survival as well in mouse models and human ICU samples with sepsis by sustaining cortisol homeostasis.[32]

We conclude that corticosteroids exert therapeutic effects in septic shock by engaging GR-dependent transcriptional regulation—primarily through the activation of anti-inflammatory genes and suppression of pro-inflammatory signaling cascades. The precision and magnitude of these responses hinge on the dynamic interplay of GR dimer/monomer status, cellular heterogeneity, and microenvironmental factors (**Fig. 1**). In recent years, a potential step

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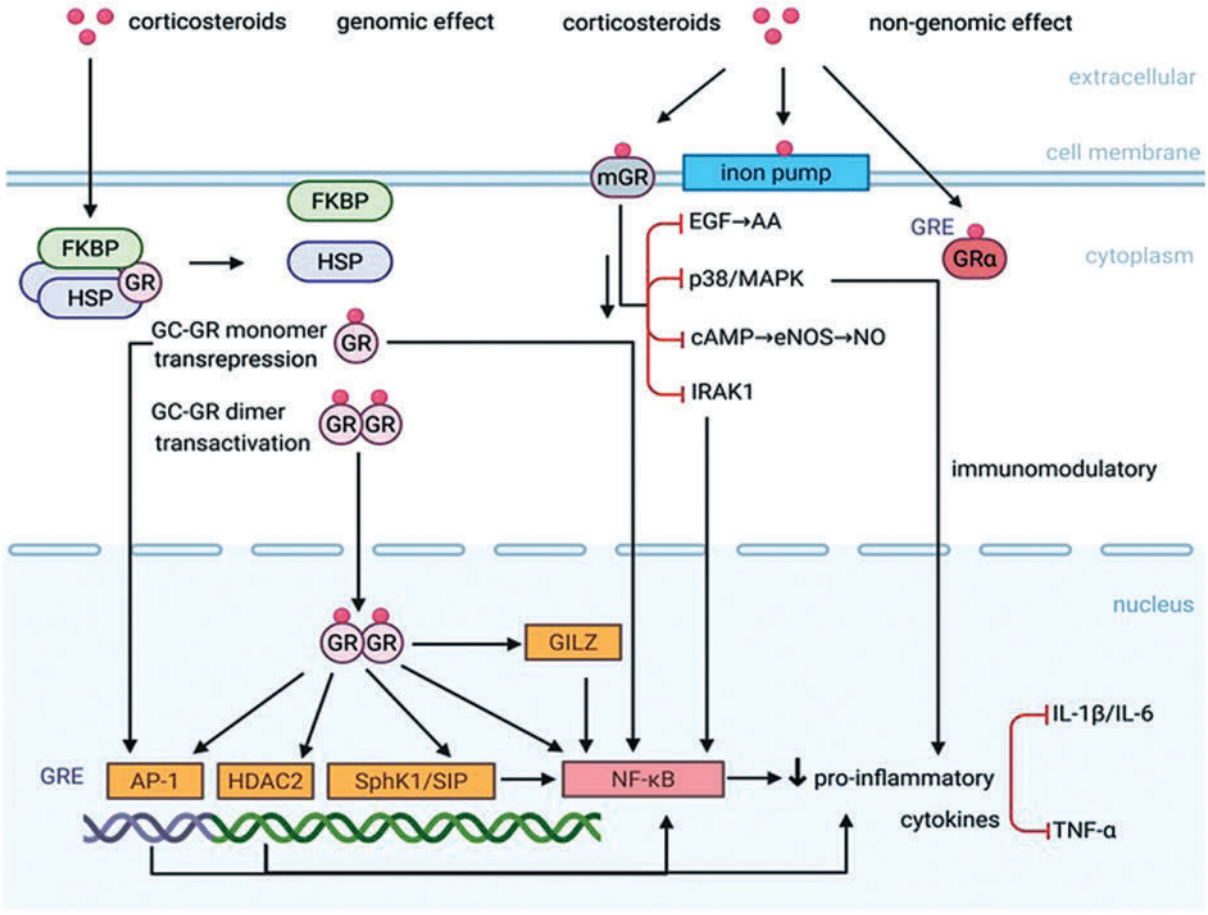

Fig. 1 Molecular mechanisms of corticosteroids in septic shock.

of tetrameric GR complexes bringing together two GC binding sites has been identified, and additional experiments may clarify its role in the regulation of inflammation.[33,34] Deciphering these mechanisms with higher resolution, particularly through gene network analyses and single-cell transcriptomic profiling, will prove indispensable for optimizing corticosteroid-based interventions and solving therapeutic resistance in septic shock.

Nongenomic Effects: Fast Inflammation Suppression and Cell Protection

Swift nongenomic responses are conducted within a few minutes after exposure to corticosteroids during septic shock. These responses operate independently of new gene transcription, leading to reduced platelet aggregation, diminished cell adhesion, suppressed intracellular phosphotyrosine kinase activity, and increased annexin 1 externalization.[19] Nongenomic effects arise by corticosteroids in three ways: nonspecific interactions with ion pumps on cellular membranes; specific interplays with cytoplasmic GRα receptor via GRE; specific interactions with membrane-bound GR through stimulating G protein and increasing cyclic adenosine monophosphate levels[35,36] (**Fig. 1**). The mechanisms underlying nongenomic effects, regulates endothelial function, vascular tone, and immune cell activation throughout septic shock's acute phase.

Experimental evidence reveals that corticosteroids mediate rapid nongenomic anti-inflammatory effects across both transformed cells and immune cells. We know that arachidonic acid (AA) and toll-like receptor 9 (TLR9) both play important roles in inflammation. It was proved that dexamethasone administration (≤1 minute) potently hindered epidermal growth factor (EGF)-stimulated AA release through a GR-dependent way, by inhibiting EGF receptor recruitment in adenocarcinoma models.[37] In dexamethasone-treated murine macrophages (≤30 minutes), GR interacted with IL-1R-associated kinase 1, thereby impeding its ubiquitination and preventing subsequent TLR9-induced NF-κB signaling activation.[38] Bhattacharyya et al found that mitogen-activated protein kinase (MAPK) phosphatase 1, a phosphatase induced by GR, deactivated p38 MAPK, resulting in decreased expression of pro-inflammatory cytokines such as TNF-α and IL-6 through macrophages-GR conditional deleted rat model.[26] What's more, Zhang et al indicated that the impaired vascular response to norepinephrine observed in the LPS-induced septic shock rat model may be restored by short-term exposure to dexamethasone through nongenomic activation of Rho-kinase activity.[39] Recently, it was suggested that corticosteroids may reprogram inflammatory macrophages into anti-inflammatory cells at the mitochondrial level, inhibiting glycolysis and hypoxia-induced factor 1α, stimulating itaconate, which counteracts succinate accumulation resulting from the stalling of the

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tricarboxylic acid cycle. These effects in restoring the mitochondrial network are mainly nongenomic via GR interaction with the pyruvate dehydrogenase.[40,41]

Pharmacological Aspects

Preclinical Findings

Based on the aforementioned molecular mechanisms, it is evident that corticosteroids exhibit anti-inflammatory and immune regulatory effects in animal models. Besides, there are still many studies in humans to elucidate the pharmacological mechanism of corticosteroids in septic shock.

Hydrocortisone (HCT) administration was observed to rapidly decrease the production of pro-inflammatory cytokines and improve hemodynamic indices such as MAP and systemic vascular resistance.[42] In critically ill patients with septic shock, administration of HCT led to significant short-term decreases in the vasopressor dependency index and improvement in cardiac power index.[43] In pediatric septic shock, low GR expression, especially combined with high cortisol, correlated with complicated clinical courses and poor outcomes, consistent with findings from transcriptional research.[44] This suggests variability in pharmacological response linked to receptor abundance. Chen et al demonstrated that dexamethasone administration significantly ameliorated pathological alterations in T lymphocytes derived from septic shock patients, specifically reversing both the impaired cellular proliferative capacity and elevated miR-155 expression levels observed in vitro-cultured specimens. This experimental evidence thereby suggested corticosteroids exert immunoregulatory effects to restore immune homeostasis via miRNA-mediated transcriptional regulation.[45]

Analysis of blood specimens from patients with septic shock revealed significantly elevated expression of glucocorticoid receptor β (GRβ), a dominant-negative isoform that antagonizes classical GRα-mediated signaling pathways. This phenomenon was observed in vivo and in vitro, contributing to the failure of suppressing TNF-α and the development of corticosteroid resistance.[46] Quantitative PCR in sepsis patients' blood showed that overexpression of GILZ transcript variant 1 correlated with poor prognosis, so corticosteroid treatment may not be suitable for specific GILZ subgroups of sepsis patients.[47]

Clinical Trials

During the early era spanning the 1970s to 1990s, clinical trials investigating high-dose corticosteroid regimens (e.g., supra-physiological doses of methylprednisolone $\geq$ 30 mg/kg) were conducted to modulate inflammatory responses in sepsis management. These interventions demonstrated accelerated shock reversal; however, subsequent analyses revealed no mortality benefit for the increased incidence of secondary infections and treatment-related complications.[48]

Subsequently, attention has shifted to the development of "low-dose" corticosteroid protocols, with increased research focus on "stress-dose" HCT administration (200–300 mg/day) combined with or without fludrocortisone (FCT) supplementation, targeting both CIRCI and vascular hyporesponsiveness. The GER-INF-05 trial demonstrated that a 7-day regimen combining HCT and FCT significantly reduced mortality risk in mechanically ventilated patients with septic shock complicated by relative adrenal insufficiency.[49] The 2008 CORTICUS trial demonstrated that HCT administration failed to significantly reduce 28-day all-cause mortality in patients with septic shock, irrespective of adrenal responsiveness to adrenocorticotropic hormone stimulation testing. While replicating the shock reversal acceleration observed in the GER-INF-05 study, the CORTICUS trial revealed a higher incidence of secondary infection after HCT.[50] At the basis of GER-INF-05, the COIITSS trial in 2010 found that the addition of FCT to HCT resulted in a statistically nonsignificant −3% absolute reduction in in-hospital mortality.[51] The HYPRESS trial failed to demonstrate, in unselected sepsis, that HCT may prevent the occurrence of vasopressor dependency.[52] The ADRENAL trial found no evidence for a significant survival benefit with HCT in septic shock, and accelerated shock resolution and reduced mechanical ventilation duration.[53] The APROCCHSS trial demonstrated that combining HCT with FCT significantly lowered 90-day mortality, hastened shock resolution without significant adverse events.[54]

The most recent systematic review concluded that, compared with placebo or usual care, corticosteroids probably increases the chance of having shock reversed on day 7:18 trials, $n = 6{,}938$, relative risk (RR): 1.22 (95% confidence interval [CI]: 1.13–1.33; $p < 0.00001$; random-effects model) and on day 28 (16 trials, 7,415, RR: 1.05; 95% CI: 1.03–1.07; $p < 0.00001$).[55] In the Cochrane review, compared with placebo or usual care, corticosteroids probably reduce 28-day mortality (RR: 0.89; 95% CI: 0.84–0.95; 22,915 participants; 72 studies; moderate-certainty evidence). Some meta-analyses increasingly dissect the marginal benefits of adding FCT, indicating a modest (RR is approximately 0.85–0.93) mortality benefit with low-dose HCT ± FCT administration in septic shock.[56–59]

Clinical Evidence of Corticosteroid Treatment in Septic Shock

Clinical Evidence on Hemodynamics

Low-to-moderate dose HCT—whether administered alone or combined with FCT—demonstrates consistent acceleration of hemodynamic recovery in adult septic shock (**Table 1**). Nevertheless, the optimal steroid dosing protocols and timing of initiation, and evidence in children, remain uncertain.

Across most RCTs, HCT regimens (200 mg/day via bolus or continuous infusion) reliably elevate MAP by 5 to 10 mm Hg within hours of administration and reduce time to vasopressor independence by 1 to 2 days.[60–63] Furthermore, an increase in vasopressor-free days by day 14 or 28 (where measured) was also observed with HCT.[64,65] Regarding the combination of HCT with FCT, the APROCCHSS trial enrolled septic shock patients predominantly from pulmonary infection, and subsequent smaller-scale investigations demonstrated statistically significant reduction in vasopressor-dependent shock duration,[54,64,66–68] along with a potential mortality benefit.[54] ADRENAL trial enrolled septic shock patients from abdominal infection showed no significant benefit in 90 day mortality.[53]

From subgroup analyses with dose, formulation, and administration modalities, a limited open-label randomized controlled trial revealed bolus administration of HCT demonstrated superior

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Table 1 Clinical evidence on hemodynamics of corticosteroid treatment in septic shock

Reference	Type and size	Population	Treatment	Hemodynamic outcome	Conclusion
[60]	Double-blind RCT; $n = 41$	Adults with late (>48 h) septic shock on catecholamines	IV HCT 300 mg/d (100 mg q8h) for 5 d vs. placebo	7-d shock reversal rate, hemodynamics	HCT group had higher shock reversal (68% vs. 21%); rapid hemodynamic improvement
[61]	Single-center RCT; $n = 40$	Adults with septic shock and high-output failure	HCT "stress doses" (100 mg loading, then continuous infusion of 0.18 mg/kg/h, after shock reversed, continuous infusion reduced to 0.08 mg/kg/h kept constant for 6 d) vs. placebo	Time to cessation of vasopressors, hemodynamics	HCT shortened the duration of vasopressor therapy
[62]	Double-blind crossover RCT; $n = 40$	Adults with septic shock	HCT (100 mg loading, then 10 mg/h × 3 d) vs. placebo	MAP, SVR, HR, NE requirement	HCT increased MAP, SVR, and reduced norepinephrine needs
[63]	Single-center RCT; $n = 58$	Adults with septic shock requiring high-dose norepinephrine	HCT 200 mg/d (50 mg every q6h): continuous infusion vs. bolus	Shock reversal rate	Shock reversal was higher in the bolus than in continuous infusion (75% vs. 44%)
[65]	Multicenter retrospective cohort; $n = 1,470$	Adults with vasopressor-dependent septic shock	Timing of HCT initiation (≥200 mg/d, mostly 50 mg IV q6h), started at one of: 0–6, 6–12, 12–24, 24–48, or >48 h after shock onset	Vasopressor-free days	Early HCT (0–6 h) was related to more vasopressor-free days
[64]	Single-center, retrospective; $n = 228$	Adults with septic shock	HCT vs. HCT + FCT; all received ≥200 mg/d HCT	Shock-free days at day 14	Combination group had more shock-free days.
[68]	Multicenter, open-label phase II RCT; $n = 153$	Adults with septic shock	IV HCT 200 mg/d (50 mg q6h) alone or plus one of three enteral FCT doses (50/100/200 μg) daily for 7 d	Time to shock resolution	No significant difference in shock reversal time; FCT absorption confirmed
[54,104]	Multicenter, RCT (APROCCHSS), $n = 1,241$	Adults with septic shock (<24 h onset)	IV HCT 200 mg/d (50 mg q6h) + FCT 50 μg orally daily, for 7 d vs. placebo	Shock resolution time, 90-d mortality	Combination group achieved faster shock resolution and lower 90-d mortality
[53]	Large international RCT (ADRENAL), $n = 3,658$	Adult ICU patients with septic shock	continuous infusion HCT 200 mg/d for 7 d or ICU discharge vs. placebo	Primary: 90-d mortality, secondary: shock recurrence, ICU discharge, ventilator duration	HCT did not reduce shock duration or recurrence; aided earlier ICU/mechanical ventilation discharge
[50]	Multicenter RCT (CORTICUS); $n = 499$	Adults with septic shock	IV HCT 200 mg/d (50 mg q6h) for 5 d, with 6-d taper vs. placebo	28-d mortality, shock reversal (24 h vasopressor-free)	Faster shock reversal, but no significant difference in mortality at 28 d
[110]	Single-center RCT; $n = 77$	Adults with refractory septic shock	IV HCT 200 mg/d vs. standard care	MAP, lactate clearance, NE requirement	MAP increased faster, and norepinephrine was discontinued earlier in the hydrocortisone group

shock reversal rates by day 7 compared with continuous infusion protocols.[63] Recent dose–response RCTs revealed no significant advantage of increasing enteral HCT doses above 50 μg per day and confirmed systemic absorption.[68] There is no conclusive evidence from subgroup analyses to support variations in HCT dosing. Most studies employed a standard dose of 200 mg/day of HCT, administered either intermittently or continuously, and direct head-to-head comparisons among differing doses are limited, particularly regarding hemodynamic stability endpoints. A retrospective study, stratified by steroid initiation timing, showed that early administration (within 6 hours of shock onset) yielded more vasopressor-free days.[65] In contrast, other RCTs generally initiated steroids within 24 to 48 hours of shock onset, yet failed to report subgroup analyses based on timing—notably, no RCTs have directly compared early versus late initiation through randomized allocation. Multiple high-quality meta-analyses have rigorously synthesized hemodynamic outcomes in septic shock: steroid regimens demonstrate a significant elevation in the proportion of patients successfully weaning from vasopressors (RR: 1.06–1.34) and vasopressor-free days by 2 days on average.[55,59,69–71]

Clinical Evidence on Respiratory Function

Adjunctive low-dose HCT therapy (with or without FCT) in adult septic shock indicated consistent efficacy in accelerating shock reversal and earlier cessation of ventilation. However, robust high-quality evidence supporting systemic improvements in pulmonary gas exchange or acute respiratory distress syndrome (ARDS) prevention remains limited, with direct respiratory outcome data provided only from a few trials and meta-analyses

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Table 2 Clinical evidence on the respiratory function of corticosteroid treatment in septic shock

Reference	Type and size	Population	Treatment	Respiratory outcomes	Conclusion
[72]	RCT; $n = 197$	Adults with early sepsis-associated ARDS ($n = 154$ with vasopressor-dependent shock)	HCT 50 mg IV q6h for 7 d vs. placebo	PaO_2/FiO_2, VFDs, organ-support-free days	Low-dose HCT improved PaO_2/FiO_2, VFDs
[73]	RCT; $n = 87$	Adults with early septic shock	High-dose methylprednisolone vs. placebo	ARDS and lung injury incidence, mortality	High-dose methylprednisolone did not prevent lung injury/ARDS
[54,104]	RCT (APROCCHSS); $n = 1,241$	Adults with septic shock (<24 h onset)	IV HCT 200 mg/d (50 mg q6h) + FCT 50 µg orally daily, for 7 d vs. placebo	Time to weaning from ventilation	HCT + FCT reduced 90-d mortality and time to wean
[53]	RCT (ADRENAL); $n = 3,800$	Adult ICU patients with septic shock	Continuous infusion HCT 200 mg/d for 7 d or ICU discharge vs. placebo	Cessation of mechanical ventilation	Steroids hastened shock reversal and earlier initial extubation
[74]	Meta analysis; 21 RCTs; n is approximately 12,350	Adults with sepsis from 21 RCTs	Various corticosteroid regimens vs. placebo	Ventilator days	Significant ventilator days decreased; no shock-stratified respiratory outcomes
[75]	Meta analysis; 5 RCTs; n is approximately 5,838	Adults with septic shock from 5 RCTs	Various corticosteroid regimens vs. placebo	Time to cessation of mechanical ventilation	Steroids reduced 28-d mortality, hastened ventilator withdrawal
[76]	Meta analysis; 21 RCTs	Adults with sepsis/septic shock from 21 double-blind RCTs	Various corticosteroid regimens vs. placebo	Mechanical ventilation duration, respiratory failure, ARDS (not shock-stratified)	No significant improvement in duration of mechanical ventilation, respiratory failure, or ARDS rates
[111]	Narrative review	–	–	Extracted VFDs and PaO_2/FiO_2 data from some RCTs	Summarizes select RCT respiratory outcomes (VFDs, gas exchange); conclusions vary by trial
[112]	RCT (VICTAS); $n = 501$	Adults with sepsis-induced respiratory and/or cardiovascular dysfunction	Vitamin C (1.5 g), thiamine (100 mg), and HCT 50 mg IVq6h vs. placebo	VFDs	No difference in VFDs. Did not specifically assess outcomes for the shock-only subgroup
[113]	Narrative review	–	–	Mortality, ventilator days	Focused on ventilation endpoint comparison
[114]	Narrative review	–	–	Ventilator days	Highlights differences from major RCTs regarding ventilator outcomes and implications

(**Table 2**). An RCT evaluated HCT effect on respiratory outcomes in sepsis-associated ARDS (mostly with shock), found that HCT (50 mg q6h for 7 days) improved the number of mechanical ventilation-free days (VFD) and PaO_2/FiO_2.[72] High-dose methylprednisolone failed to prevent ALI in patients with early septic shock.[73] HCT combined with FCT significantly reduced the time to wean patients off ventilation.[66] ADRENAL trial found that the HCT group achieved earlier cessation of mechanical ventilation, and did not report on respiratory function parameters or occurrence of ARDS.[53] Systematic reviews and meta-analyses suggested HCT shortened the duration of dependency on mechanical ventilation or rapid weaning from ventilatory support.[74–76]

Clinical Evidence on Kidney Function

Preclinical studies showed that corticosteroids had inhibitory effects on renal inducible nitric oxide synthase activity following endotoxemia, thereby preventing hypoxic cortical injuries, enhancing renal oxygen delivery efficiency, reducing mitochondrial damage, and ultimately reversing acute kidney injury (AKI) in sepsis.[77–80] High-dose corticosteroids were thought to transiently worsen renal function.[81] ADRENAL, APROCCHSS and VANISH trials provided inconclusive data on the effects of HCT on incidence/duration of renal replacement therapy (RRT), AKI and renal recovery.[53,54,82] Observational studies found that early or late steroid initiation did not demonstrate a clear renal benefit either.[83–86] Likewise, addition of FCT did not significantly alter renal endpoints relative to HCT alone.[84] Meta-analysis suggested a trend toward reduced RRT with early steroid initiation.[87] In a post hoc analysis of the ADRENAL trial, HCT therapy was associated with a reduced risk of new RRT requirement.[88] It is worth noting that existing research and meta-analyses often include chronic kidney disease (CKD) patients or lack explicit exclusion of CKD when analyzing corticosteroid effects on kidney outcomes (**Table 3**).

Clinical Evidence on Liver

Corticosteroids demonstrated a liver-protective effect across varying inflammation levels in septic shock rats. Notably, the

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Table 3 Clinical evidence on renal function of corticosteroid treatment in septic shock

Reference	Type and size	Population	Treatment	Kidney outcomes	Conclusion
[81]	RCT; $n = 382$	Adults with severe sepsis or septic shock	High-dose methylprednisolone	Creatinine, blood urea nitrogen (BUN)	BUN was increased from baseline ($p < 0.1$)
[54]	RCT (APROCCHSS); $n = 1,241$	Adults with septic shock (<24 h onset)	IV HCT 200 mg/d (50 mg q6h) + FCT 50 μg orally daily, for 7 d vs. placebo	RRT	Renal (kidney) endpoints are secondary, not conclusive
[53]	RCT (ADRENAL); $n = 3,658$	Adult ICU patients with septic shock	Continuous infusion HCT 200 mg/d for 7 d or ICU discharge vs. placebo	RRT	No RRT benefit
[88]	RCT (VANISH); $n = 409$	Adult with septic shock (vasopressor-dependent, ≤6 h)	Vasopressin or norepinephrine ± HCT 200 mg/d (50 mg q6h) vs. placebo	AKI/RRT	Results regarding steroids and renal outcomes inconclusive
[83]	Prospective cohort; $n = 81$	Adult with septic shock	HCT initiation from diagnosis: the early group (within 3 h) and the late group (after 3 h)	RRT	No difference in RRT rate
[84]	Retrospective cohort; $n = 251$	Adult with septic shock, refractory to fluids/vasopressors	HCT (≥200 mg qd IV) + FCT (50–100 μg oral) vs. HCT alone	RRT	No difference in RRT between groups
[85]	Retrospective cohort; $n = 198$	Adults with septic shock on vasopressors	Early HCT (<12 h after vasopressors) vs. late HCT (>12 h after vasopressors)	RRT	No significant difference in RRT
[86]	Retrospective cohort; $n = 351$	ICU adults with sepsis or septic shock and cortisol testing	HCT 200 mg/d empiric or indicated vs. placebo	AKI, RRT	Not associated with improved RRT or renal recovery
[87]	Meta analysis; 7 RCTs; $n = 3,063$	Adult with septic shock from 7 RCTs	Early vs. late initiation of low-dose HCT (doses variable)	CRRT/RRT	No clear renal (CRRT/RRT) benefit
[88]	Post hoc cohort study; $n = 3,161$	Adults with septic shock	HCT 200 mg/d vs. placebo	RRT	Associated with a reduced risk of new RRT

high-inflammation group exhibited a more pronounced therapeutic response, characterized by significant reductions in pro-inflammatory cytokines and diminished phosphorylation levels of p38 MAPK and NF-κB.[89] Despite extensive research on corticosteroids in septic shock, very few high-quality studies directly report liver-related outcomes, and available data suggest that high-dose corticosteroids may transiently worsen hepatic laboratory markers without clinical benefit.[81] Patients randomized to HCT treatment (200 mg/day) exhibited a markedly faster decline in SOFA scores from day 0 to 7, notably driven by improvements in liver dysfunction ($n = 499$, $p < 0.0001$) in CORTICUS.[90] No trial reported severe liver events (acute liver failure, need for liver support, and liver-specific mortality).[91]

Clinical Evidence on Endothelial Function and Coagulation

Septic shock is characterized by dysregulated inflammation, endothelial injury (loss of barrier, glycocalyx shedding, and leukocyte adhesion), and an accompanying immunothrombotic coagulopathy (platelet consumption, D-dimer rise, and disseminated intravascular coagulation). The direct impact of corticosteroids on endothelial integrity and the coagulation cascade remains incompletely defined. Despite supporting mechanistic and clinical signals, there remains a lack of integrated animal or clinical data on the effects of corticosteroids on endothelial function and coagulation in septic shock.

HCT demonstrated a protective effect on the endothelial glycocalyx from TNF-induced injury in an animal model.[92] In adults with septic shock, HCT reduced soluble E-selectin levels, suggesting enhanced endothelial function.[62] In critically ill COVID-19 patients who frequently experience glycocalyx damage, the beneficial effects of steroids in alleviating endothelial injury are well-documented.[93]

Clinical Evidence on Immune Function

Low-to-moderate dose (200–300 mg/day) of HCT treatment in septic shock consistently accelerates shock reversal while dampening the early surge of hyper-cytokinemia and endothelial/neutrophil activation that hallmark the hyperinflammatory phase (**Table 4**). This intervention demonstrates consistent hemodynamic benefits by raising MAP through suppression of NO-mediated vasodilation.[62,94] Regardless of the dose regimen, corticosteroid treatment is followed by a rapid and significant reduction in circulating IL-6 and IL-8 levels,[42,62,95] and TNF-α and IL-1β concentrations.[42,96] Effects on anti-inflammatory cytokines, such as IL-10, remained variable or minimal—some trials reported declines, while others demonstrated no measurable change.[62,97] The effects of HCT on cellular immunity are fairly variable, with trials showing heightened CD4+ T cell apoptosis, and studies showing either suppression or negligible alteration.[98,99] The monocyte HLA-DR expression and innate phagocytic capacity remain largely unaltered,[42,96] whereas neutrophil activation markers—CD11b,

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Table 4 Clinical evidence on renal function of corticosteroid treatment in septic shock

Reference	Type and size	Population	Treatment	Immune end-points	Conclusion
[62]	Double-blind RCT, $n = 40$	Adults with septic shock	HCT (100 mg loading, then 10 mg/h × 3 d) vs. placebo	IL-6, IL-8, IL-10, sTNFR-I/II, NOx, CD11b/CD64	Decrease: IL-6/8/10,E-selectin, CD11b, CD64, T-helper cells, eosinophil, basophil granulocytes; increase: IL-12/IFN-γ, monocytes; no change: total granulocyte and leukocyte counts
[95]	Double-blind RCT, $n = 12$	Patients with human septic shock	HCT (loading dose of 100 mg then continuous infusion of 0.18 mg/kg/h for 6 d) vs. placebo	IL-8, PMN-E, S-100B	Decrease: IL-8; no change: PMN-E, S-100B
[115]	Parallel RCT, $n = 40$	Patients with early hyperdynamic septic shock	Low-dose HCT (50 mg bolus then continuous infusion of 0.18 mg/kg/h, after shock reversal reduced to 0.06 mg/kg/h) vs. placebo	IL-6, IL-8, IL-10	Decrease: IL-6, IL-8; no change: IL-10
[97]	Double-blind RCT, $n = 24$	Adult septic shock with high-output circulatory failure	HCT "stress doses" (50 mg bolus then continuous infusion of 0.18 mg/kg/h) vs. placebo	IL-6, IL-8, IL-10, TNF-α	Decrease: IL-6, IL-8; no change: IL-10, TNF-α
[116]	RCT, $n = 57$	Adult with septic shock	HCT 200 mg/d vs. placebo	CD4+ T cell apoptosis (Annexin-V)	Increase: CD4+ T cell apoptosis
[96]	Observational, $n = 29$	Severe sepsis patients (sepsis shock subgroup concluded)	HCT 200 mg/d vs. placebo	LPS-stim PBMC cytokines, HLA-DR	Decrease: IL-12, TNF-α; no change: HLA-DR
[42]	Prospective cohort, $n = 105$	Adult with severe sepsis	HCT 200 mg/d vs. placebo	IL-1β, IFN-γ, TNF-α, IL-6; phagocytosis	Decrease: all cytokines; no change: phagocytosis
[99]	RCT, $n = 60$	Adult with septic shock	Standard care + early goal-directed therapy + with/without HCT	CD4+ T cell count, CD8+ T cell count, ratio of CD4+ T cell and CD8+ T cell	Increase: count of CD4+ and CD8+ T cells. Ratio of CD4+ T cells and CD8+ T cells
[98]	RCT, $n = 60$	Adult with septic shock	Early vs. late ow-dose corticosteroid treatment	IL-6, CD4+ T cell apoptosis	Decrease: IL-6, CD4+ T cell apoptosis

CD64, PMN elastase—decline significantly yet exhibit no definitive functional consequences.[62,95] The VANISH trial underscored these profound hemodynamic and cytokine-modulating effects. Post hoc transcriptomic analyses compellingly reveal divergent outcomes: patients harboring the "immunocompetent" sepsis response signature (SRS2) exhibit marked therapeutic gains, while those with the "immunosuppressed" SRS1 endotype paradoxically experience excess mortality.[100,101] So gene expression-based scoring for immune state may guide whether corticosteroids are harmful or beneficial.[102]

Corticosteroids in septic shock effectively suppress systemic inflammatory markers and restore hemodynamic stability, yet concurrently trigger adaptive immunosuppression—potentially exacerbating risks in immunosuppressed transcriptomic subgroups.

Clinical Evidence on Mortality

The landscape of high-quality randomized evidence on corticosteroid treatment in adult septic shock is primarily shaped by two landmark trials. ADRENAL found no significant reduction in 90-day or 6-month all-cause mortality compared with placebo with a continuous-infusion HCT regimen (200 mg/day).[66,103] APROCCHSS study—using q6 intravenous 50 mg bolus of HCT plus enteral 50 μg FCT for 7 days—demonstrated significant survival benefits that persisted from 90 days out to 180 days.[54,104] Several systematic reviews and meta-analyses integrate these RCTs with smaller-scale investigations. The 2025 update of the Cochrane review on corticosteroids for sepsis in children and adults found that compared with placebo or usual care, corticosteroids probably reduce 28-day mortality (RR: 0.89; 95% CI: 0.84–0.95; 22,915 participants; 72 studies; moderate-certainty evidence) and in-hospital mortality (RR: 0.90; 95% CI: 0.84–0.97; 17,459 participants; 40 trials; moderate-certainty evidence), and may result in little to no difference in long-term mortality (RR: 0.97; 95% CI: 0.91–1.03; 8,468 participants; 12 studies; low-certainty evidence).[55] Other meta-analyses that include HCT-only regimens confirm a modest short-term benefit (RR is approximately 0.90) but fail to detect a clear advantage beyond 90 days, largely because ADRENAL contributes the majority of long-term person-time and the neutral outcome.[75,105,106]

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Reviews focusing on the combination of HCT-FCT showed a 9 to 12% relative reduction in 28-day mortality and reported a similar effect on "long-term" mortality, that is, at 90 to 180 days.[59] A Bayesian network meta-analysis also reported benefit in 28- or 30-day mortality of the dual-steroid protocol without extending to long-term outcomes.[57] Meta-analyses suggest potential heightened benefits in vasopressor-dependent patients or those with elevated APACHE-II scores, though most observed interactions were post hoc analyses lacking robust statistical validation.[75,105] In the Cochrane review, subgroup analyzes did not suggest that the response to treatment this may be influenced by types of corticosteroids (test for subgroup differences: $\chi^2 = 3.33$, df = 5 [$p = 0.65$], $I^2 = 0\%$), dose/duration (long course of low dose vs. short course of high dose, test for subgroup differences: $\chi^2 = 0.00$, df = 1 [$p = 0.97$], $I^2 = 0\%$) or mode (continuous vs. intermittent bolus administration test for subgroup differences: $\chi^2 = 1.17$, df = 1 [$p = 0.28$], $I^2 = 14.6\%$). In metaregression analyses, the lower the dose given on day 1 ($p = 0.0263$), the lower the cumulated dose ($p = 0.0227$), and the longer the duration of treatment ($p = 0.041$), the lower the RR for dying at 28 days.[55] Subgroup analyses based on factors related to participants, suggested no evidence of differences in response to treatment between children and adults (test for subgroup differences: $\chi^2 = 0.34$, df = 1 [$p = 0.56$], $I^2 = 0\%$), and greater likelihood of survival benefits from corticosteroids in septic shock (RR for dying at 28 days 0.93; 95% CI: 0.86–1.00; $p = 0.04$; 8,871 participants; 29 studies; $\chi^2 = 35.95$, df = 28 [$p = 0.14$]; $I^2 = 22\%$; random-effects model), sepsis complicated by ARDS (RR: 0.59; 95% CI: 0.42–0.83; $p = 0.002$; 496 participants; 5 studies; $\chi^2 = 4.72$, df = 4 [$p = 0.32$]; $I^2 = 15\%$; random-effect model), Covid 19 (RR: 0.88; 95% CI: 0.81–0.95; $p = 0.002$; 7,764 participants; 7 studies; $\chi^2 = 3.93$, df = 6 [$p = 0.69$]; $I^2 = 0\%$; random-effect model) or secondary to community acquired pneumonia (RR: 0.68; 95% CI: 0.54–0.86; $p = 0.001$; 3,818 participants; 16 studies; $\chi^2 = 13.07$, df = 14 [$p = 0.52$]; $I^2 = 0\%$; random-effect model), as compared with uncomplicated unselected sepsis (test for subgroup differences: $\chi^2 = 16.05$, df = 4 [$p = 0.003$], $I^2 = 75.1\%$).

In summary, the short-term benefits of the HCT + FCT combination are consistently demonstrated, while the long-term mortality advantage remains uncertain. Rigorous RCTs have failed to show significant benefits, and meta-analyses are constrained by limited long-term endpoints and substantial heterogeneity (**Table 5**).

Clinical Evidence on Long-Term Sequels

Adjunctive low-to-moderate dose corticosteroids significantly reduce the dependency on life-supportive therapies and may improve short-term survival in sepsis. Available evidence suggested possible complications among adult and pediatric

Table 5 Clinical evidence on mortality of corticosteroid treatment in septic shock

Reference	Type and size	Population	Treatment	Short-term mortality	Long-term mortality
[53]	RCT (ADRENAL); $n = 3,800$	Adult ICU patients with septic shock	Continuous infusion HCT 200 mg/d for 7 d or ICU discharge vs. placebo	No benefit in 90-d mortality	No benefit in 6-mo mortality
[54,104]	Original RCT (APROCCHSS); $n = 1,241$	Adults with septic shock (<24 h onset)	IV HCT 200 mg/d (50 mg q6h) + FCT 50 µg orally daily, for 7 d vs. placebo	Significant benefit in 90-d mortality	Significant benefit in 180-d mortality
[117]	Meta-analysis; 61 RCTs; *n* is approximately 12,192	Adults and children with sepsis	Various corticosteroid regimens vs. placebo	Slightly reduce 28-d mortality	Very uncertain
[59]	Meta analysis; 4 RCTs; *n* is approximately 2,050	Adult with septic shock from 4 RCTs	Various corticosteroid regimens vs. placebo	Significantly reduced 28-d mortality (RR is approximately 0.88)	Significantly reduced long-term mortality (RR is approximately 0.9), not specifying the exact day of "long-term"
[105]	Meta analysis; 30 RCTs; *n* is approximately 8,836	Adults with sepsis or septic shock from 30 RCTs	Various corticosteroid regimens vs. placebo	Significantly reduced 28-d mortality (RR is approximately 0.9)	No significant reduction long-term mortality at day 90/d 180/1 y
[75]	Meta analysis; 5 RCTs; *n* is approximately 5,838	Adults with septic shock from 5 RCTs	Various corticosteroid regimens vs. placebo	Significantly reduced 28-d mortality	No significant reduction long-term mortality at day 90/1 y
[106]	Meta analysis; 13 RCTs; *n* is approximately 5,838	Adults with septic shock from 13 RCTs	Various corticosteroid regimens vs. placebo	No significant reduction in 28-d mortality	Not reported
[57]	Meta analysis; 18 RCTs; *n* is approximately 95,800	Adults with vasopressor-dependent septic shock from 18 RCTs	Various corticosteroid regimens vs. placebo	Significantly reduced 28-d/30-d mortality with HCT + FCT (OR: 0.79)	Not reported

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survivors receiving corticosteroids, spanning neuromuscular weakness, neuropsychiatric deficits, glycemic dysregulation, gastrointestinal hemorrhage, hypernatremia, cerebrovascular events, myocardial infarction, secondary infections, and skeletal system sequelae.[55,71,107] Crucially, the long-term sequels for these survivors remain uncertain, demanding longitudinal investigation.

The only long-term evidence originates from two single-center trials performed more than 20 years ago, both of which suggested that low-to-moderate dose HCT therapy administered during septic shock correlated with a reduced prevalence of posttraumatic stress disorder within 3 to 6 months and an enhanced quality of life.[108,109] These findings are widely cited in systematic and narrative reviews, yet remain unsubstantiated by replication studies.

Conclusion

Septic shock remains a life-threatening condition characterized by alarmingly high mortality rates. Corticosteroids exert a beneficial role in clinical management through both genomic and nongenomic mechanisms, as evidenced by a variety of clinical and preclinical research. Moreover, this treatment, especially HCT, has been demonstrated to significantly reduce mortality rates, enhance shock reversal rates, increase VFD, and improve organ support outcomes in patients with septic shock.

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Statements and Additional Information

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